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Synthesis of polychlorinated biphenyls (PCBs) using the Suzuki-coupling

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Abstract

An improved synthesis of polychlorinated biphenyls (PCBs) utilizing a palladium-catalyzed cross-coupling reaction (Suzuki-coupling) is described. The coupling of (chlorinated) aryl boronic acids **1–3** with bromochlorobenzenes **4** using the standard conditions of the Suzuki-coupling gave the desired PCB congeners **5–7** in good to excellent yields. The self-coupling product of the aryl boronic acids is the major impurity of this reaction. 3,4,5-trichlorophenyl derivatives such as **10** can be synthesized by coupling of an aryl boronic acid with the corresponding bromochloroaniline **8**. The approach offers the advantage of high selectivity and good yields compared to conventional methods such as the Cadogan reaction and allows the use of less toxic starting materials.

Keywords: Environmental contaminants; Biaryls; PCB; Cross-coupling; Palladium

1. Introduction

Polychlorinated biphenyls (PCBs) are persistent and wide-spread environmental contaminants (Hansen, 1987, 1994, 1999). Their lipophilic character and their resistance to degradation contribute to the tendency of PCBs to accumulate in the food chain, where they represent an environmental and human health hazard (Hansen, 1999). PCBs' mechanisms of toxicity are varied and still poorly understood, in part because technical PCB products consist of complex mixtures of many of the 209 possible PCB congeners. Studies of the biological effects of PCBs as well as studies of their chemical transport, degradation and remediation greatly benefit from the availability of single congeners. Unfortunately, the (large scale) synthesis of many PCB congeners is difficult, and many PCB congeners are only poorly characterized.

Numerous reactions have been utilized for the synthesis of PCBs, including the Ullmann reaction (Fanta, 1974), the Sandmeyer reaction (Nakatsu et al., 1982) and the Cadogan reaction (Cadogan et al., 1962), which is a modification of the Gomberg Bachmann reaction (Hutzinger et al., 1983). These and related reactions have significant drawbacks. The Ullmann reaction is generally limited to symmetrical PCB congeners and results in significant amounts of highly toxic dibenzofuran byproducts (Moron et al., 1973). The Cadogan reaction is more versatile, but is a very low yield procedure (10–20%), and the by-products of this reaction are not well characterized. The Sandmeyer reaction can be used to synthesize several symmetrical PCB congeners, for example 2,2′,5,5′-tetra-, 3,3′,4,4′-tetra- and 2,2′,4,4′,5,5′-hexachlorobiphenyl, from benzidine derivatives (Nakatsu et al., 1982). However, benzidine is a known human carcinogen and chlorinated benzidines are classified as possible human carcinogens (please see: http://ehis.niehs.nih.gov/roc/toc8.html).

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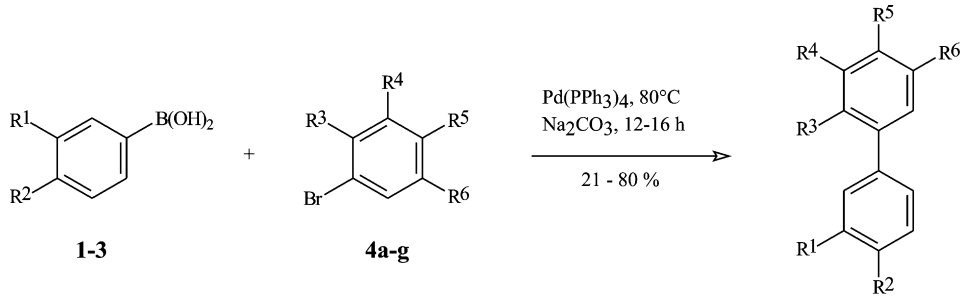

1-3 **4a-g** **5a-c, 6b,d,g, 7c,e,f-g**

1: $R^1 = R^2 = H$
2: $R^1 = Cl, R^2 = H$
3: $R^1 = H, R^2 = Cl$

4a: $R^3 = Cl$
4b: $R^4 = Cl$
4c: $R^5 = Cl$
4d: $R^3 = R^4 = Cl$
4e: $R^3 = R^5 = Cl$
4f: $R^4 = R^5 = Cl$
4g: $R^4 = R^6 = Cl$

5a: $R^3 = Cl$
5b: $R^4 = Cl$
5c: $R^5 = Cl$
6b: $R^1 = R^4 = Cl$
6d: $R^1 = R^3 = R^4 = Cl$
6g: $R^1 = R^4 = R^6 = Cl$
7c: $R^2 = R^5 = Cl$
7e: $R^2 = R^3 = R^5 = Cl$
7f: $R^2 = R^4 = R^5 = Cl$
7g: $R^2 = R^4 = R^6 = Cl$

Fig. 1. Synthesis of PCB congeners.

Over the last decades numerous biphenyl syntheses have emerged and are now standard reactions in organic chemistry (Miyaura and Suzuki, 1995; Stanforth, 1998; Suzuki, 1999). Only few of these reactions were used to synthesize PCB congeners or PCB metabolites. We recently described the preparation of several mono- and dihydroxylated PCB metabolites with the Suzuki-coupling (Bauer et al., 1995; McLean et al., 1996). The cross-coupling of 4-chloro phenoltriflate with benzene boronic acid in the presence of lithium chloride was utilized to synthesize 4-chlorobiphenyl (Huth et al., 1989). In a similar reaction, 4-chlorobiphenyl was prepared employing the corresponding 4-chloro organozinc compound instead of the boronic acid and $Pd(dppf)_2Cl_2$ (dppf = 1,1′-bis(diphenylphosphino) ferrocene) as a catalyst. The palladium-catalyzed cross-coupling of arenediazonium salts (Sengupta and Bhattacharyya, 1997) or hypervalent aryliodonium species (Kang et al., 1996a,b) with phenylboronic acids was also used to synthesize 4-chlorobiphenyl. Despite the great need for single PCB congeners for biological and environmental studies, the scope of these reactions has never been extended to synthesize other and higher chlorinated PCB congeners (Fig. 1).

Based on our experience with the synthesis of dihydroxylated PCB metabolites, we investigated the Suzuki-coupling of phenylboronic acid (**1**) and two chlorinated benzeneboronic acids (**2–3**) with several bromochlorobenzenes **4** (Miyaura and Suzuki, 1995). As expected, 2- (**5a**), 3- (**5b**) and 4-chlorobiphenyl (**5c**), important lower chlorinated PCB congeners, can easily be synthesized using 3 mol% of $Pd(PPh_3)_4$ as a catalyst and 2 M sodium carbonate as a base (Table 1) (Bauer et al., 1995). All PCB congeners were pre-purified by passing them through a short Al_2O_3 column with *n*-hexanes or petroleum ether as the eluent.

Higher chlorinated di- (**6b**, **7c**) and trichlorobiphenyls (**6d**, **6g**, **7e–g**) were also synthesized selectively in good yields using the same reaction conditions (see Table 1). The trichlorobiphenyl compounds listed in Table 1 are difficult to synthesize by other methods such as the Cadogan coupling and are therefore hardly studied in biological systems. For example, the Cadogan- (Mullin et al., 1984) and the Ullmann coupling (Parkinson et al., 1980) were used to synthesize 2,4,4′-trichlorobiphenyl (**7e**) resulting in three and two product mixtures, respectively. The Suzuki-coupling now allows us to synthesize large quantities of 2,4,4′-trichlorobiphenyl (**7e**) in a single step. Also, the introduction of one *ortho*-chloro substituent did not pose a problem under the reaction conditions investigated, as shown for 2-chloro- (**5a**), 2,3,3′-trichloro- (**6d**), and 2,4,4′-trichlorobiphenyl (**7e**). The synthesis of *ortho*-substituted PCB congeners is of particular interest because their toxicity is poorly understood (Hansen, 1999).

The synthesis of PCB congeners with three chlorine substituents in one phenyl ring is limited because only a few trichloroanilines are available from commercial sources. However, 3,5-dichloro- or 3,4,5-trichlorobiphenyls can be synthesized in moderate yields by coupling a chlorinated benzeneboronic acid (**3**) with 4-bromo-2,6-dichloroaniline (**8**). The 4-aminobiphenyl **9** is obtained after column chromatography over alumina. 3,4′,5-Trichloro- (**7g**) and 3,4,4′,5-tetrachlorobiphenyl (**10**) were obtained from the 4-aminobiphenyl derivative **9** by deamination with phosphoric acid or by Sandmeyer reaction, respectively (Fig. 2).

For biological and toxicological studies it is not only important to have pure compounds, but also to know which impurities are present. Fortunately, side reactions of the Suzuki reaction, such as hydrolytic deboronation

Table 1
Synthesis of PCB congeners

PCB		Boronic acid	Arylbromide	Yield (crude yield) (%)	Purity (crude)[a]	m.p.[b] (°C)	m.p. (Lit.)[c] (°C)
5a	2	**1**	**4a**	61 (88)	>99.8 (>98)[d]	27	34
5b	3	**1**	**4b**	37 (89)	>99.8 (>96)[e]	Oil	16.5
5c	4	**1**	**4c**	72	>97	69–70[f]	77.7
6b	3,3′	**2**	**4b**	80 (82)	>97	oil	–
6d	2,3,3′	**2**	**4d**	66 (92)	>97 (>90)	41–42	–
6g	3,3′,5	**2**	**4g**	71 (84)	>98 (>95)	78–79	–
7c	4,4′	**3**	**4c**	63 (87)	>99	148–149	148–149
7e	2,4,4′	**3**	**4e**	2[g] (98)	>99	50–52	57–58
7f	3,4,4′	**3**	**4f**	58 (70–85)	>98 (>96)	80–81	86.8–87.8
7g	3,4′,5	**3**	**4g**	94	>98 (>92)	84–85	88
10	3,4,4′,5	–		–	97.5	152–153	–

[a] The purity of all compounds was analyzed with a Hewlett–Packard 5890 A Gas Chromatograph equipped with a FID detector and a HP-1 (methyl silicone gum) column (Hewlett–Packard, Avondale, PA). Please see text for a discussion of the major impurities.
[b] Determined with a MEL-TEMP apparatus.
[c] See Erickson, 1986.
[d] The crude product contained 2-chlorobiphenyl and biphenyl in a 55:1 ratio.
[e] The crude product contained 3-chlorobiphenyl and biphenyl in a 125:1 ratio.
[f] Purity > 99.5% (from MeOH).
[g] Small scale reaction (2.5 mmol of 4-ClPhB$(OH)_2$).

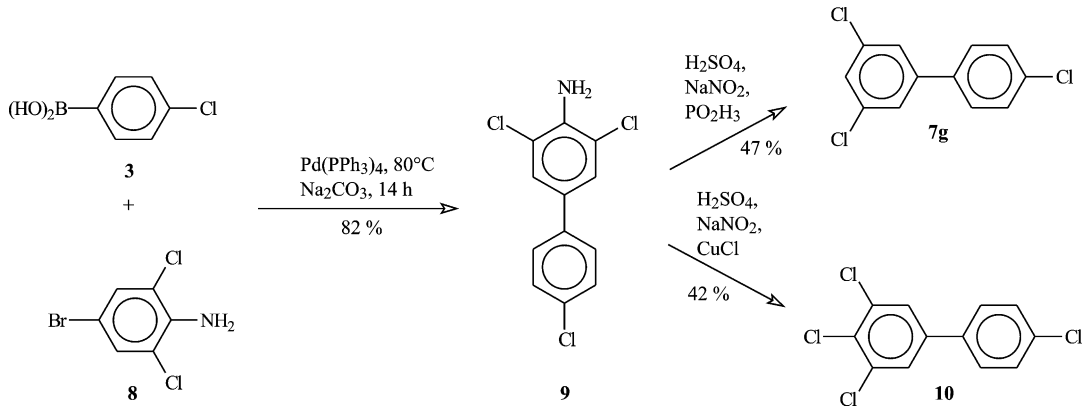

Fig. 2. Synthesis of 3,4′,5-trichloro and 3,4,4′,5-tetrachlorobiphenyl.

(Muller and Fleury, 1991; Fukuyama et al., 1993), aryl–aryl exchange between the palladium center and the phosphine ligand (Kong and Cheng, 1991; O'Keefe et al., 1992; Segelstein et al., 1995) and self-coupling of aryl boronic acids (Moreno-Mañas et al., 1996; Smith et al., 1997; Aramendia and Lafont, 1999), are well studied. All PCB congeners synthesized by the Suzuki-coupling showed one major impurity that can be removed by several recrystallizations from methanol or fractional destilation. GC–MS analysis, retention time comparison and co-injection with authentic standards revealed that this major impurity is the self-coupling product of the boronic acid. This side reaction is a result of traces of oxygen which can only be excluded by using freeze thaw cycles (Wallow and Novak, 1994).

We conclude that application of the Suzuki methodology to the synthesis of PCB congeners has great advantages over conventional methods. Studies to extend the synthesis to higher chlorinated PCB congeners and to reduce the homocoupling of the boronic acids are currently underway in our laboratory.

2. Experimental

All PCB congeners were characterized by ^{1}H and ^{13}C NMR, FT–IR and GC/MS spectroscopy. The IR spectra were obtained using a Nicolet Magna-IR 560 Spectrometer E.S.P. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400S NMR Spectrometer by using $CDCl_3$ (Cambridge Isotope Laboratories, Andover, MA) as solvent and TMS as internal standard unless otherwise noted. Combustion analysis of all PCB congeners were performed by Atlantic Microlab (Atlanta, GA). Deviations are smaller or equal $\pm 0.34\%$. GC/MS analysis were performed in the Mass Spectrometry Facility of the University of Kentucky (Lexington, KY). The purity of all compounds was analyzed with a Hewlett–Packard 5890 A Gas Chromatograph equipped with a HP-1 (methyl silicone gum) column (Hewlett–Packard, Avondale, PA) and determined based on relative peak area. The following conditions were used for the gas chromatographic analysis: injector: 255°C, detector (FID): 300°C, starting temperature: 40°C final temperature: 245°C, heating rate: 10°/min. The melting points were determined on a MEL-TEMP apparatus and are uncorrected. All solvents were obtained from commercial sources and used without further purification. *Caution*. PCBs are reasonably anticipated to be human carcinogens and should therefore be handled in an appropriate manner.

2.1. 2,6-Dichloro-4-bromoaniline (8) (Godfrey and Thrift, 1967)

m.p. = 86°C (white needles from ethanol, >98% by GC). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.29 (br s, NH_2, 2H), 7.28 (s, ArH, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 107.89, 119.96, 130.19 (2 × C), 139.39. IR (cm^{-1}): 3424, 3301, 1615, 1467, 857. MS m/z (relative intensity, %): 239/241/243 (33), 160 (5), 124 (9), 88 (7), 61 (18), 43 (100).

2.2. Synthesis of PCB congeners, general procedure of the Suzuki-coupling (Bauer et al., 1995; McLean et al., 1996)

Sodium carbonate (5 ml, 2 M aq.) was added to a solution of a chloro-bromobenzene (5 mmol) and $Pd(PPh_3)_4$ (0.18 mg) in toluene (20 ml). A solution of a chlorobenzene boronic acid (5 mmol) in ethanol (10 ml) was added slowly to the solution of the bromo benzene under a nitrogen atmosphere. The reaction mixture was maintained at 80°C for 12–16 h. Hydrogenperoxide (0.5 ml, 30%) was added slowly to the warm reaction mixture to destroy unreacted boronic acid. The mixture was

Table 2
Analytical data of PCB congeners

PCB	IR (cm^{-1})	MS-EI *e/z* (Int.)[a]	^1H NMR[b]
5a	1467, 1425, 1036, 748, 699	188 (100, $C_{12}H_9Cl^{\cdot+}$), 152 (30, M-HCl)	7.13 (“t”, $J \approx 7.6$ Hz, d, $J = 2.0$ Hz, 4-H), 7.17 (“t”, $J \approx 7.4$, d, $J = 1.6$ Hz, 4-H), 7.23–7.40 (m, 3,6,2′,3′,4′,5′,6′-H)
5b	1593, 1565, 1473, 753, 696	188 (100, $C_{12}H_9Cl^{\cdot+}$), 152 (30, M-HCl)	7.32 (d, $J = 8.0$ Hz, “t”, $J = 2.0$ Hz, 4-H), 7.34–7.41 (m, 4′,5-H), 7.42–7.49 (m, 3′,5′,6-H), 7.54–7.60 (m, 2,2′,6′-H)
5c	1478, 1098, 832, 758, 688	188 (100, $C_{12}H_9Cl^{\cdot+}$), 152 (30, M-HCl)	7.32–7.45 (m, 3,3′,4,4′,5,5′-H), 7.47–7.55 (m, 2,2′,6,6′-H)
6b	1592, 1384, 1101, 775, 718	222 (100, $C_{12}H_8Cl_2^{+}$), 186 (8, M-HCl), 152 (69, M-Cl_2)	7.29–7.42 (m, 4,4′,5,5′,6,6′-H), 7.51 (“s”, 2,2′-H)
6d	1388, 774, 692	256 (100, $C_{12}H_7Cl_3^{+}$), 220 (4, M-HCl), 186 (33, M-Cl_2), 150 (10)	7.20 (d, $J = 8.0$ Hz, d, $J = 1.6$ Hz, 4-H), 7.25 (t, $J = 8.0$ Hz, 5-H), 7.26–7.30 (m, 4′-H), 7.35–7.38 (m, 5′,6′-H), 7.38–7.40 (m, 2′-H), 7.48 (d, $J = 8.0$ Hz, d, $J = 1.6$ Hz, 6-H),
6g	1583, 1553, 854, 782, 682	256 (100, $C_{12}H_7Cl_3^{+}$), 220 (4, M-HCl), 186 (33, M-Cl_2), 150 (10)	7.35–7.42 (m, 4,4′,5′,6′-H), 7.43 (d, $J = 2.0$ Hz, 2,5-H), 7.53 (m, 2′-H)
7c	1474, 1088, 1002, 815, 702	222 (100, $C_{12}H_8Cl_2^{+}$), 186 (8, M-HCl), 152 (65, M-Cl_2)	7.40 (AA‘XX’ system, 3,3′,5,5′-H), 7.48 (AA‘XX’system, 2,2′,6,6′)
7e	1465, 807, 734, 730, 541	256 (100, $C_{12}H_7Cl_3^{+}$), 220 (5, M-HCl), 186 (48, M-Cl_2), 150 (15)	7.24 (d, $J = 8.4$ Hz, 6-H), 7.31 (d, $J = 8.4$ Hz, d, $J = 2.0$ Hz, 5-H), 7.34 (AA‘XX’ system, 3′,5′-H), 7.41(AA‘XX’ system, 2′,6′-H), 7.50 (d, $J = 2.0$ Hz, 3-H)
7f	1461, 1091, 807	256 (100, $C_{12}H_7Cl_3^{+}$), 220 (4, M-HCl), 186 (33, M-Cl_2), 150 (10)	7.33 (d, $J = 8.0$ Hz, d, $J = 2.0$ Hz, 6-H), 7.37–7.45(AA‘BB’ system, 2′,3′,5′,6′-H), 7.47 (d, $J = 8.0$ Hz, 5-H), 7.59 (d, $J = 2.0$ Hz, 2-H)
7g	1555, 1495, 1093, 822, 800	256 (100, $C_{12}H_7Cl_3^{+}$), 220 (5, M-HCl), 186 (42, M-Cl_2), 150 (12)	7.28 (t, $J = 1.2$ Hz, 4-H), 7.35 (d, $J = 1.2$ Hz), 7.38 (s, 2′,3′,5′,6′-H)
10	1430, 1091, 828, 813, 802, 491	290 (100, $C_{12}H_6Cl_4^{+}$), 254 (3, M-HCl), 220 (40, M-Cl_2), 150 (12, M-Cl_4)	7.41 (s, 2′,3′,5′,6′-H), 7.53 (s, 2,6-H)[c]

[a] The observed fragmentation patters (M–HCl, M–Cl_2 and M–Cl_2–HCl) are in agreement with literature data (Safe and Hutzinger, 1972).
[b] The ^1H chemical shifts of previously uncharacterized PCB congeners were assigned based on the paper of Yanagisawa et al. (1987).
[c] Recorded on a Varian Gemini 200 (200 MHz).

Table 3
^{13}C chemical shifts of PCB congeners[a]

PCB	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
5a	140.46	132.43	131.30	128.44	126.74	129.86	139.32	127.97	129.37	127.52	129.37	127.97
5b	143.08	127.84	134.65	127.24[b]	129.95	125.28	139.81	127.10	128.87	127.29[b]	128.87	127.10
5c	139.62	128.35	128.87[b]	133.34	128.87[b]	128.35	139.94	126.95	128.85[b]	127.56	128.85[b]	126.95
6b	141.54	127.86[b]	134.78	127.22[b]	130.10	125.22	141.54	127.86[b]	134.78	127.22[b]	130.10	125.22
6d	140.84	131.02	133.72[c]	129.28[b]	127.24	129.89	141.36	129.39	133.98[c]	127.51	129.35[b]	128.07
6g	142.70	125.61	135.43	127.75[b]	135.43	125.61	140.28	128.47	135.01	127.20[b]	130.26	125.21
7c	138.42	128.20	129.03	133.76	129.03	128.20	138.42	128.20	129.03	133.76	129.03	128.20
7e	137.91	133.23	131.90	134.12[c]	127.28	129.85	136.69	128.44	130.69	134.12[c]	130.69	128.44
7f	139.91	128.75	132.97	131.78	130.77	126.13	137.14	128.15	129.15	134.30	129.15	128.15
7g	142.91	125.47	135.43	127.47	135.43	125.47	136.95	128.30	129.23	134.71	129.23	128.30
10[d]	139.94	127.01	134.62	134.90	134.62	127.01	136.12	128.15	129.33	130.57	129.33	128.15

[a] The ^{13}C chemical shifts of previously uncharacterized PCB congeners were assigned based on the data published by Yanagisawa et al. (1986).
[b] Assignment may be interchangeable with each other.
[c] Signals overlap.
[d] Recorded on a Varian Gemini 200 (50 MHz).

stirred at room temperature for additional 4 h and diluted with diethyl ether (30 ml). The reaction mixture was extracted once with NaOH (10 ml, 2 M aq.) and three times with water (20 ml). The organic phase was dried over $MgSO_4$ and the solvents were removed under reduced pressure. Column chromatography (glass column, 300 mm × 25 mm i.d.) over Alumina (Alumina Adsorption 80–200 mesh, Fisher Scientific, Pittsburg, PA) with *n*-hexanes or petroleum ether as eluent yielded the desired PCB congener.The analytical data of all PCB congeners are summarized in Tables 1–3.

2.3. 3,3′,4′,5-Tetrachloro-4-aminobiphenyl (9)

m.p. = 128°C (>99%). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.96 (br s, $-NH_2$, 2H), 6.98–7.16 (m, ArH, 6H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 119.93, 126.15 (CH), 127.50, 128.98, 130.34, 133.19, 137.29, 139.46. IR (cm^{-1}): 3420, 3310, 2921, 2850, 1474, 1384, 1309, 1094, 1084, 1013. MS m/z (relative intensity, %): 271/273/275/277 (100), 201 (18), 129 (52), 83 (36), 69 (53), 57 (53).

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